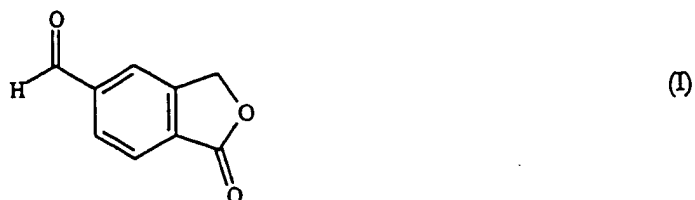


CLAIMS

1) A process for the preparation of citalopram which comprises:

(a) treating 5-formylphthalide of formula

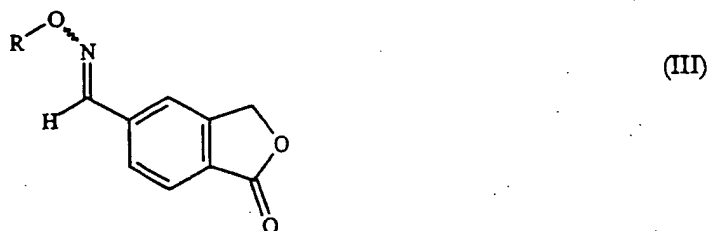


with a hydroxylamine of formula



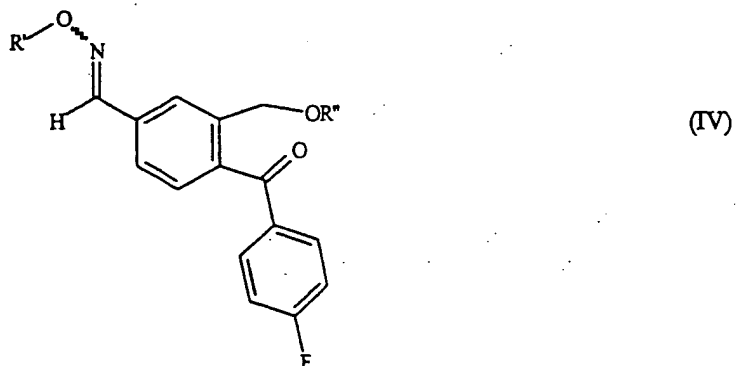
wherein R represents a hydrogen atom (IIa) or a substituent R' inert under the conditions of a Grignard reaction (IIb);

(b) reacting the oxime thus obtained of formula



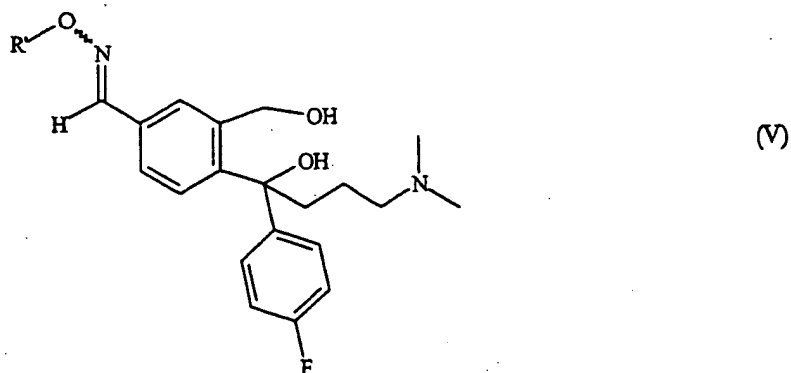
wherein R is as defined above, with a 4-fluorophenylmagnesium halide, straightforwardly when R=R' (IIIb) or after substitution of R by R' when R=H (IIIa);

(c) reacting the intermediate ketone of formula



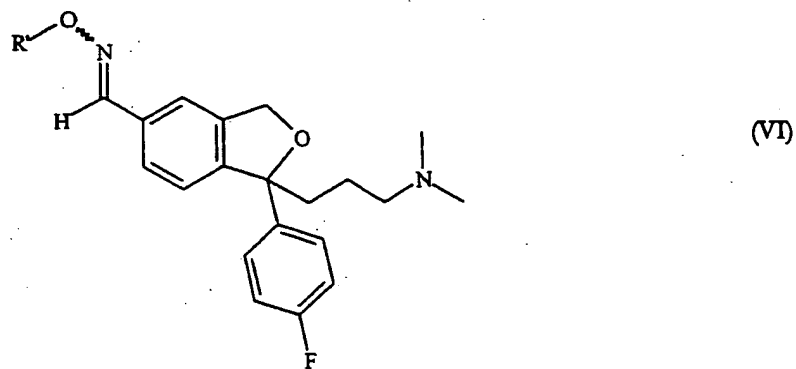
wherein R' is as defined above and R'' represents MgHal (IVa) wherein Hal is halogen, or hydrogen (IVb), with a [3-(dimethylamino)propyl]magnesium halide;

(d) cyclizing the intermediate diol of formula



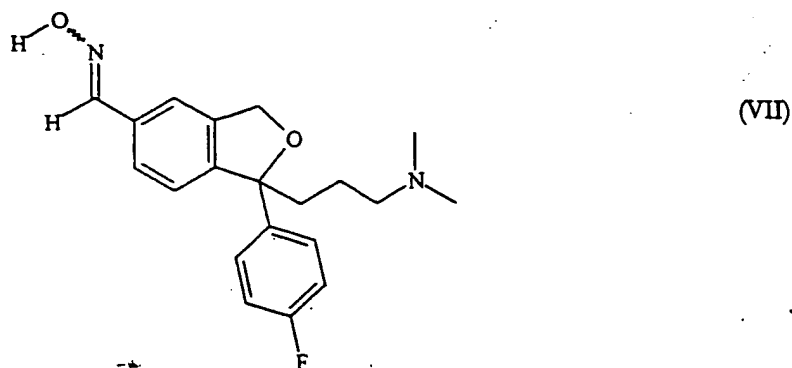
wherein R' is as defined above;

(e) removing the group R' of the substituted oxime of formula



wherein R' is as defined above; and

(f) converting the unsubstituted oxyimino group of the oxime of formula



into nitrile to give citalopram (A) or one of its pharmaceutical acceptable salts; or

(e') optionally, when R' is triphenylmethyl or diphenylmethyl, straightforwardly converting the substituted oxyimino group of the oxime of formula VI into nitrile by treatment with a mixed anhydride of formula



wherein R''' represents a C₁-C₆ alkyl group, an aralkyl group or an aryl group, to give citalopram (A) or a pharmaceutical acceptable salt thereof.

- 2) The process according to claim 1, wherein R' is (C₁-C₆)alkyl, (C₁-C₃)alkoxy(C₂-C₄)alkyl, a benzyl, diphenylmethyl or triphenylmethyl group, unsubstituted or substituted on the benzene rings with one or more groups independently chosen among (C₁-C₆)alkyl, (C₁-C₃)alkoxy and nitro groups or with a 2,3- or 3,4-methylenedioxy group.
- 3) A process according to claim 2 wherein R' is triphenylmethyl or diphenylmethyl.
- 4) A process according to claim 1 wherein said 4-fluorophenylmagnesium halide is the bromide
- 5) A process according to claim 1 wherein said [3-(dimethylamino)propyl]magnesium halide is the chloride.
- 6) A process according to claim 1 wherein step (d) is carried out in the presence of a halide of an alkyl- or arylsulfonic acid.
- 7) A process according to claim 6 wherein said halide of an alkyl- or arylsulfonic acid is methanesulfonyl chloride.
- 8) A process according to claim 1 wherein R' represents triphenylmethyl or diphenylmethyl and the intermediate of formula VI is straightforwardly converted to citalopram according to step (e').
- 9) A process according to claim 8 wherein in said anhydride of formula VIII R''' represents (C₁-C₆)alkyl, benzyl or phenyl.
- 10) A process according to claim 9 wherein R''' represents methyl.
- 11) A process according to claim 10 wherein said anhydride of formula VIII is used in admixture with acetic acid.
- 12) A process according to claim 11 wherein said mixture is prepared from formic acid and acetic anhydride in a molar ratio of 1:1.25.
- 13) A process according to claim 1 wherein said compound of formula VIII is used in 1.25 moles per mole of compound of formula VI.
- 14) A process according to claim 1 wherein citalopram is isolated in the form of hydrobromide.
- 15) A compound of formula III, wherein R represents hydrogen or a substituent R' inert under the conditions of a Grignard reaction.
- 16) A compound according to claim 15 wherein R represents a substituent R' selected between triphenylmethyl and diphenylmethyl.

- 17) A compound of formula IV wherein R' represents hydrogen or a substituent inert under the conditions of a Grignard reaction and R'' represents MgHal (IVa), wherein Hal is halogen, or hydrogen (IVb).
- 18) A compound according to claim 17 wherein R' is triphenylmethyl or diphenylmethyl.
- 19) A compound of formula V wherein R' represents hydrogen or a substituent inert under the conditions of a Grignard reaction.
- 20) A compound according to claim 19 wherein R' is triphenylmethyl or diphenylmethyl.
- 21) A compound of formula VI wherein R' represents a substituent inert under the conditions of a Grignard reaction, other than methyl.
- 22) A compound according to claim 21 wherein R' is triphenylmethyl or diphenylmethyl.
- 23) Use of the compounds of formula III, IV, V and VI as intermediates for the preparation of citalopram.
- 24) A process for preparing citalopram, according to claim 1, as a single enantiomer characterized in that the corresponding isolated enantiomers of the compounds of formula V or VI are used as intermediates.
- 25) A process according to claim 24, characterized in that the isolated enantiomers of compounds of formula V or VI are prepared by resolution of the corresponding racemic mixtures with optically active acids, preferably with tartaric or camphorsulfonic acid.
- 26) A compound according to claims 19 to 22 as a single enantiomer.